

NUT Midline Carcinoma Masquerading As a Thymic Carcinoma

Introduction

Thymic carcinomas are rare tumors that arise from the epithelium of the thymus gland and characterized by cytologic atypia, invasiveness, and high risk of relapse and death.¹⁻³ The current WHO schema recognizes at least 11 histologic subtypes.⁴⁻⁷ Undifferentiated thymic carcinoma is one of the subtypes that can be indistinguishable from other poorly differentiated carcinomas such as NUT midline carcinoma (NMC).⁸ Despite the aggressive nature of both diseases, a correct diagnosis is important because of the recent development of targeted therapies for NMCs. Herein we describe two cases of a particularly aggressive form of disease and discuss the differential diagnosis of these lesions.

Case Report 1

The first patient was a 22-year-old African American/Asian college-age woman whose pertinent history began approximately 3 months before she presented to the hospital. At that time, the patient began to experience mild exertional dyspnea. Because she had recently moved from Indiana to Florida, she at first attributed the symptoms to her altered work environment. The patient eventually sought medical attention and was prescribed inhalers for suspected reactive airway disease; the symptoms worsened. Chest x-ray showed mediastinal widening and chest computed tomography (CT) imaging revealed a large mediastinal mass. The patient came to Indiana University for further work-up and evaluation.

At admission, the patient reported shortness of breath with mild exertion, nonproductive cough for several weeks, and a 5-lb weight loss. The patient denied fever or chills and had no headaches, syncope, dizziness, bone pain, nausea, or vomiting. The clinical examination was unremarkable except for decreased breath sounds and slight dullness to percussion on the left. Her routine laboratory work-up was unremarkable. A chest CT scan showed a mediastinal mass that had significantly increased in 1 month (Fig 1). There was bulky confluent pretracheal and subcarinal lymphadenopathy with compression of the distal carina and left main stem bronchus. An open mediastinal biopsy was performed after the failure of a CT-guided biopsy. This showed a poorly differentiated carcinoma most likely consistent with thymic carcinoma (histologic features to be described). Flow cytometry from tissue obtained revealed T cells and polyclonal B cells and no immunophenotypic evidence of malignancy. A staging CT scan showed no evidence of metastatic disease. The patient obtained a partial response after six cycles of carboplatin and paclitaxel. Neither surgery nor radiation was performed because of the size and location of the lesion.

Six months after the completion of chemotherapy, the patient presented with marked dyspnea at rest. Chest x-ray and CT scan confirmed tumor recurrence. Salvage chemotherapy with cisplatin, doxorubicin, and cyclophosphamide was begun, and the patient re-

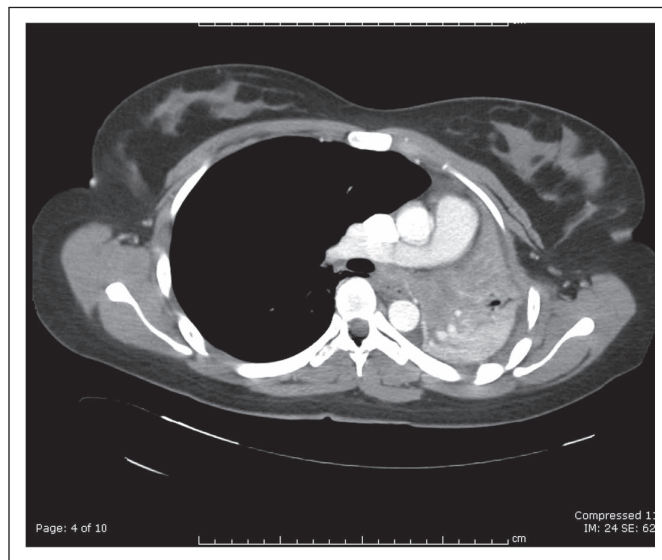


Fig 1.

sponded well. Left pneumonectomy with mediastinal lymphadenectomy was performed. During the recovery period, the patient developed neurologic symptoms and was found to have cystic cerebellar metastases on CT (Fig 2A) and magnetic resonance imaging scans (Fig 2B). She underwent resection of this lesion and received radiotherapy to her chest and her head. The patient did well for about a year, but then she was admitted to a local hospital for syncope and cardiac arrest and died soon afterward.

Case Report 2

The second patient, a 37-year-old white woman, was experiencing bronchitis and back pain; the latter she attributed to the care of an 11-year-old child with severe cerebral palsy. She had recently been diagnosed with pneumonia and had significant pleuritic pain in the right upper back and paravertebral region. Routine chest x-ray showed right middle lobe atelectasis and a 4.6-cm right paratracheal mass. Additionally, extensive mediastinal and right hilar lymphadenopathy was seen on chest CT (Fig 3). A needle biopsy suggested the diagnosis of thymoma. However, clinical suspicion of lymphoma led to mediastinoscopic biopsy. Flow cytometry of the biopsy sample was limited by low cellularity but showed polyclonal B cells and mature T cells. Following a surgical pathology consultation, a definitive diagnosis of thymic carcinoma was made (histologic features to be described).

The patient came to Indiana University for further management of thymic carcinoma. Evaluation of her CT scan showed extensive middle mediastinal disease as well as an anterior mediastinal mass. The patient was found to have baseline thrombocytopenia and was treated with carboplatin and paclitaxel. She received four cycles of

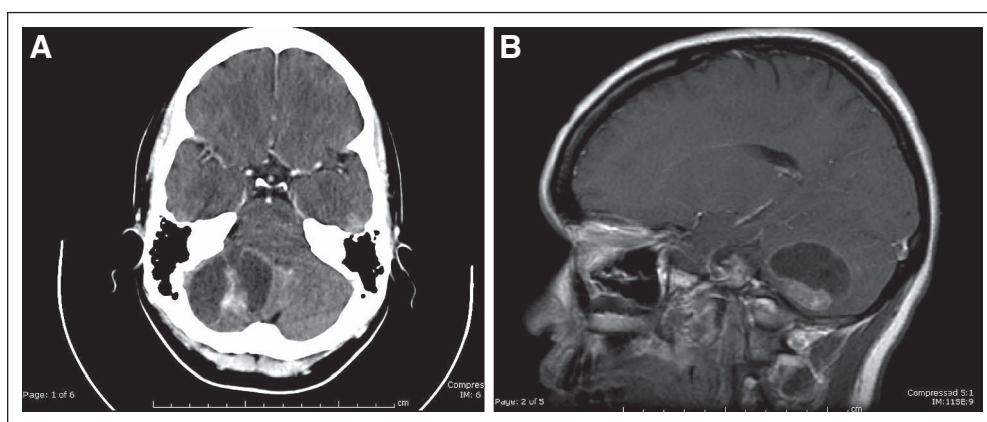


Fig 2.

carboplatin plus paclitaxel for thymic carcinoma but had to discontinue therapy because of persistent and nonresolving pancytopenia that was believed to be of autoimmune etiology. She developed paresthesias of her left jaw, which were confirmed to be metastases by fine-needle aspiration biopsy. Metastases to pleura, left shoulder, hip, and vertebral column (Fig 4) were also detected. Brain magnetic resonance imaging with and without contrast showed diffuse cerebral meningeal metastases as well as diffuse bone metastases. She underwent palliative radiation therapy and was discharged to hospice 6 months after diagnosis, where she died shortly afterward.

Histologic features. The histologic features of both patients were similar. The tumors were composed of mixed undifferentiated small cells with foci of squamous differentiation (Fig 5). The small-cell components lacked the features that are typically associated with small-cell carcinoma of the lung; that is, no nuclear molding and high mitotic and apoptotic activity. Abrupt foci of squamous differentiation characterized by small islands of cells with keratinized, pink cytoplasm were scattered within the tumors. The squamous cells had bland, nuclear features and did not show mitotic activity. The tumor cells demonstrated immunoreactivity for CD5 and cytokeratin cock-

tail, whereas synaptophysin, CK20, and CK7 were negative. Areas of squamous differentiation were highlighted by an antibody against high-molecular-weight cytokeratin (34 β E12). The tumor cells expressed NUT protein, confirming the diagnosis of NMC (Fig 6).

Discussion

NMC, also called carcinoma with t(15;19) translocation, is a variant of poorly differentiated squamous cell carcinoma that is characterized by chromosomal rearrangement of the *NUT* gene located on chromosome 15.⁹ The classic chromosomal rearrangement consists of translocated *NUT* gene in-frame with BRD4, a ubiquitously expressed transcriptional coactivator. This translocation is not present in some cases of NMC, which are referred to as NUT variants. Instead, a pairing of NUT with BRD3 is noted.¹⁰ In a small number of cases, the molecular basis is not yet understood. Although NMCs have been

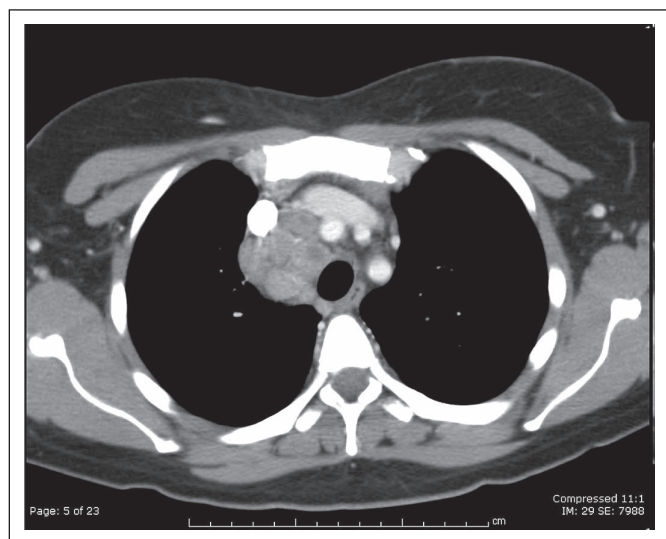


Fig 3.

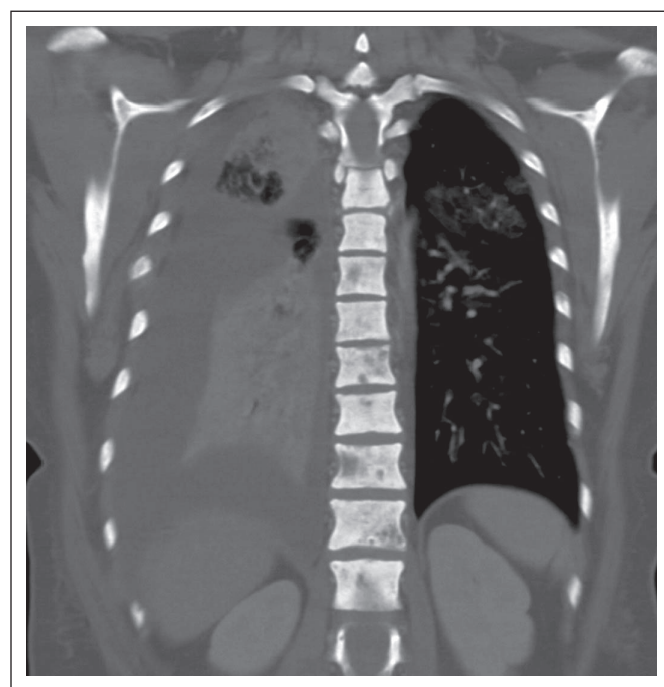


Fig 4.

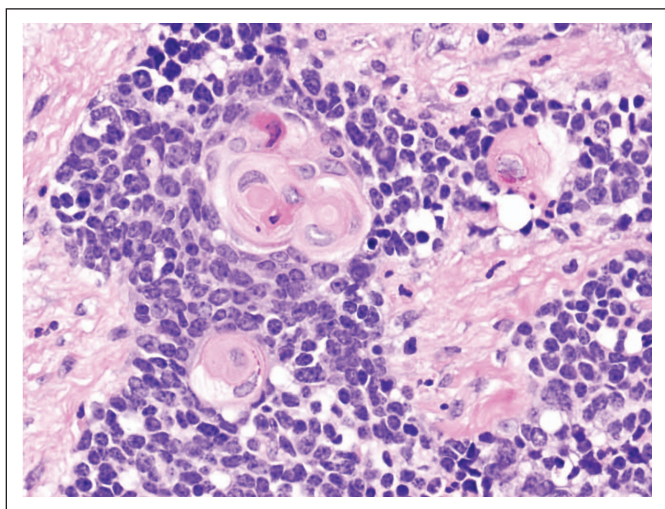


Fig 5.

classically described in children and adolescents, they have also been reported in adults.^{9,11} NMC is a poorly recognized entity both because of the location of the tumors and the histologic features.⁹ The tumors are often located in the midline and confused with sinonasal carcinomas and lung carcinomas. Histologically, the tumors are composed of a variable mix of primitive, undifferentiated cells and squamous cells. The predominance of the former leads to the misdiagnosis of small blue cell tumors (Ewing sarcoma, neuroblastoma, small-cell carcinoma), whereas the latter leads to the misdiagnosis of poorly differentiated carcinoma or squamous cell carcinoma. The recent development of an immunohistochemistry assay for NUT protein has led to increased recognition of NMCs in adults.¹⁰

In both of the patients we describe, the tumors were predominantly composed of primitive, undifferentiated cells within which foci of abrupt squamous differentiation were identified. Neither undifferentiated complements resembled classical small-cell carcinoma. In addition, neuroendocrine markers, which are typically positive in small-cell carcinoma, were not expressed by the tumor cells. The

expression of NUT protein enabled a definitive diagnosis to be made in both of these patients.

The clinical course in both patients was aggressive, leading to death within 18 months of initial diagnosis. This is consistent with the clinical behavior described in the literature for NMCs. In the series by Bauer et al,⁹ the progression-free survival (PFS) of 25 adult patients was 4% at 1 and 2 years. The overall survival (OS) was 16% and 5% at 1 and 2 years, respectively. In this large series, there was no status difference in PFS or OS by patient age, sex, tumor histology, lymph node involvement, or the exact type of translocation.

One of the patients presented here had thrombocytopenia, which was thought to be of autoimmune origin. This is unusual for patients with thymic carcinoma; myasthenia and autoimmune syndromes are more typical in thymomas.

The optimal treatment for patients with NMC is unclear. Although a number of therapeutic regimens have been used, the overall effectiveness of chemotherapy is questionable. In the series by Bauer et al,⁹ gross total resection was associated with improved survival (both PFS and OS). Intriguingly, these tumors seem to respond well to early administration of radiotherapy. Recent laboratory studies have suggested that the NUT fusion protein results in aberrant histone acetylation and blockade of differentiation. Efforts have been made to develop targeted therapeutic approaches such as direct acting inhibitors of BRD3 and BRD4 bromodomain (BETi) and histone deacetylase inhibitors (HDACi).^{12,13} A phase I clinical trial of BETi (GlaxoSmithKline, Philadelphia, PA) is available to patients with NMC. Additionally, HDACi demonstrated promising clinical response in pediatric patients.¹⁴

In summary, NMC is an increasingly recognized lesion that can be diagnosed by immunohistochemistry for NUT protein. This in turn will lead to recognition of adult cases and a full spectrum of clinical and pathologic features. The tumors tend to be aggressive, and it seems that surgery and radiation-based regimens might be optimal. Novel therapies such as HDACi and BETi are being developed to treat this rare form of cancer. These recent developments emphasize the importance of including NMC in the differential diagnosis for patients with poorly differentiated carcinomas that arise in close proximity to the midline.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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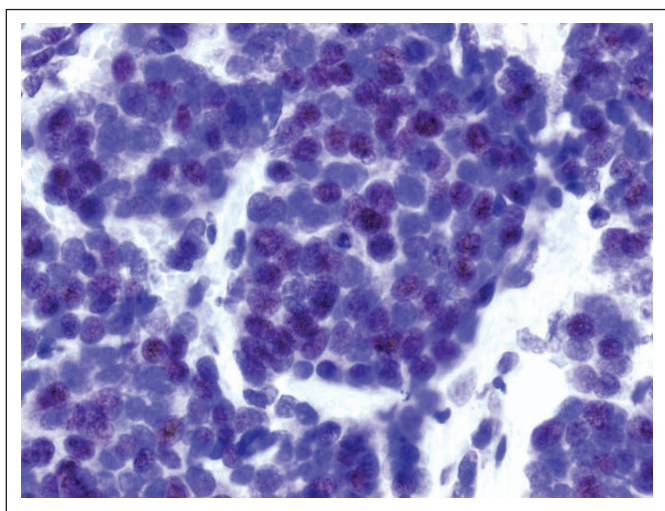


Fig 6.

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